An Evaluation of Prophylactic Treatments to Prevent Post Traumatic Joint Stiffness

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Disclosures:

Introduction: Post-traumatic arthrofibrosis impairs joint function for many orthopaedic patients. Arthrofibrosis results from both intra-articular adhesion formation and capsuloligamentous contracture. Adhesions and contractures can form by inflammation induced fibrosis which is furthered by joint immobilization(2). After damage to a joint, inflammatory cells invade the synovium and release inflammatory mediators. These mediators enact cellular changes which can lead to arthrofibrosis(1). Fibroblasts in inflamed tissue have been shown to produce high levels of alpha smooth muscle actin (α-SMA) in comparison to normal fibroblasts. Since α-SMA is associated with cellular contraction, it is proposed that such fibroblasts differentiate into contractile myofibroblasts and are responsible for shortening the tissues(6). This study evaluated agents which might provide prophylaxis against arthrofibrosis by targeting components of the inflammatory process: 1. oral montelukast (leukotriene inhibitor) 2. intra-articular injections of forskolin (blocks TGF-β1)(4) 3. intra-articular injections of triamcinolone acetonide (steroid). We hypothesized that, by blunting the effect of inflammatory mediators, each of these treatments would limit fibrosis and thus joint stiffness.

Methods: 48 male rats were placed into four groups: control (CTL), montelukast (MLK), forskolin (FSK), and steroid (STR). An incision was made medial to the right patella. The patella was dislocated laterally. The medial and lateral condyles and the trochlea were scraped 6 times each with a scalpel. The capsule was repaired with a 3-0 chromic suture (proinflammatory). The knee was immobilized in full flexion with a #2 Ethibond suture (Ethicon, Inc., Somerville, NJ), tied around the midfemur and midtibia. The skin was closed with wound clips. Group CTL received no treatment. Group MLK received 3.75 mg/kg/day montelukast (Cayman Chemical, Ann Arbor, MI) administered on their food. Group FSK received two 0.6 mg/kg intra-articular injections of forskolin (Sigma Aldrich, St. Louis, MO). Group STR received two 0.68 mg/kg intra-articular injections of triamcinolone (MedVet Supplies Mettawa, IL). Injections were performed on post-operative days 1 and 4. Rats were euthanized on the fourteenth day after surgery as it has been shown that contracture in this model levels off after 2 weeks(5). Both hind legs were disarticulated at the hip. The femorotibial angle (FTA) was measured in the right leg with the immobilization suture intact using x-ray. The immobilization suture and musculature of both legs were then removed. Remaining FTAs were measured with a 0.015-Nm extension moment applied to the joint. The FTA was measured with the joint capsule intact (intact knee), after the posterior capsule was cut (capsule cut), and with both cruciate ligaments cut (ligaments cut). Angles were normalized by subtracting the non-immobilized leg’s FTA from that of the immobilized leg. Means and standard deviations were calculated. A one way analysis of variance (ANOVA) was used to evaluate the data followed by Holm-Sidak mean comparison (Sigmastat, Systat Software Inc., Chicago, IL).

Results: Table 1 displays the means +/− 1 SD for the normalized FTA angles for each of the three measurements. On the intact knee measurements, MLK, FSK, and STR all formed significantly less contracture than CTL (p<0.05). Group STR formed significantly less contracture than MLK and FSK (p<0.05). For capsule cut measurements, MLK, FSK, and STR again all formed significantly less contracture than CTL (p<0.05). Group STR again formed significantly less contracture than MLK and FSK (p<0.05). For ligament cut measurements, CTL, MLK, and FSK did not statistically differ. However, STR formed significantly less contracture than CTL, MLK, and FSK (p<0.05).

Discussion: The control group developed a 32 degree contracture indicating that the surgical procedure successfully induced fibrosis.
Montelukast: Rats receiving oral montelukast therapy had a significant reduction in stiffness in the intact knee measurements, demonstrating on average 12 degrees more extension of the operative leg than the rats in CTL. This suggests that montelukast had a prophylactic effect against capsular contracture. MLK’s capsule cut measurements also demonstrated a significant 9 degrees more extension than the rats in CTL, indicating an effective reduction in stiffness.
Forskolin: In the intact knee measurements, rats in FSK had 10 degrees more extension than rats in CTL. This suggests that forskolin effectively reduced capsular contracture. Forskolin treated rats also had a significant 8 degrees more extension than rats in CTL with the capsule cut. This demonstrates that forskolin had a prophylactic effect against stiffness after the capsule was cut. A conservative dose of forskolin was used in this study, so it may be that increasing the dose would yield a larger effect.
Triamcinolone: Triamcinolone injections markedly reduced stiffness in the intact knee measurements demonstrated by the 24 degrees greater extension in group STR than in CTL. In fact group STR only developed a 7 degree loss of extension. Steroid injections also significantly reduced knee stiffness in the capsule cut measurements, where group STR had an average 23
degrees more extension than group CTL. Group STR is the only group in which the ligament cut measurement varied significantly from CTL. These results suggest steroids were very effective in reducing arthrofibrosis. Rats receiving steroid injections did lose a significant amount of body weight (18% of start weight). The steroid dose used corresponds to a human dose of 0.11 mg/kg based on calculations modeled by Reagan-shaw(3). Such a dose should not cause unwanted effects in humans (equivalent to 7.7mg in a 70kg human). It must be considered that a single dose or a lower dose may have a beneficial effect on arthrofibrosis without systemic effects.

This study utilized an established model of immobilization induced joint contracture modified to include trauma and presumably adhesion formation. In addition clinically applicable treatments were used in hopes that such modalities could eventually be studied clinically. All three agents resulted in significant reductions in joint stiffness but triamcinolone was significantly more effective than forskolin or montelukast. It would seem appropriate that further studies should evaluate increased doses of the novel treatments montelukast and forskolin in hopes of increased efficacy as well as evaluating lower doses of steroid to reduce side effects.

Significance: This study shows the ability of novel treatments (montelukast and forskolin) to prophylactically treat joint stiffness, and demonstrates that intra-articular steroid injections have remarkable potential to inhibit arthrofibrosis. With further research these treatments could allow physicians the ability to limit joint stiffness.

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<table>
<thead>
<tr>
<th>Group</th>
<th>Mean FTA- Intact Knee (°)</th>
<th>Mean FTA- Capsule Cut (°)</th>
<th>Mean FTA- Ligaments Cut (°)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTL</td>
<td>32 ± 5</td>
<td>28 ± 4</td>
<td>18 ± 7</td>
</tr>
<tr>
<td>MLK</td>
<td>20 ± 8</td>
<td>19 ± 7</td>
<td>12 ± 7</td>
</tr>
<tr>
<td>FSK</td>
<td>22 ± 11</td>
<td>20 ± 8</td>
<td>10 ± 9</td>
</tr>
<tr>
<td>STR</td>
<td>7 ± 9</td>
<td>5 ± 10</td>
<td>-3 ± 8</td>
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